# Reflections on the Scientific Sessions

*Following PHA's International PH Conference and Scientific Sessions in Indianapolis on June 20–22, 2014, a group of clinicians gathered by phone to discuss the highlights of the meeting they would take to their practice. Guest editor Anna R. Hemnes, MD, Assistant Professor of Medicine and Assistant Director, Pulmonary Vascular Center at Vanderbilt University and Chair of the Scientific Sessions, facilitated the call. Discussants were Raymond Benza, MD, Cardiovascular Institute, Allegheny General Hospital, Pittsburgh; Karen Fagan, MD, University of South Alabama, Mobile; Steven M. Kawut, MD, MS, Penn Cardiovascular Institute, University of Pennsylvania School of Medicine, Philadelphia; Jeffrey S. Sager, MD, MSc, Santa Barbara, CA; and Glenna Traiger, RN, MS, CNS-BC, Pulmonary Hypertension Program, UCLA.*

**Dr Hemnes:** My goal today was basically to talk about the scientific sessions and the conference and what everybody's thoughts were. I think there were 1,580 registrations for the conference, which was tremendously successful. My first question for the group, and I think everybody could answer this, was that at the end of every CME evaluation that we fill out, the question that gets asked is, what are you going to change about your practice, and what's your take home message from this meeting? While I think very little from the scientific sessions is really ready to take home to our practice, but let's say what from the conference made the greatest impression for us. What was the most prominent thing you took home from the conference?

**Dr Benza:** To me, the conference again was a wonderful opportunity to share in the collegiality of the group, which we know is fairly unique to the pulmonary hypertension community. You know, the ability to see friends and colleagues and interact with them face-to-face in a supportive and casual atmosphere surrounded by the patients we treat is a truly unique experience. And also the ability to pass on practical information to large numbers of patients is one of the most valuable experiences I've had as a practicing clinician. Every time I come back from that meeting, I feel re-oriented in why I do what I do and feel very charged at the end of the day. That renewal, energy, and enthusiasm not only help me take care of my patients better, but also allow me to conduct my research with more vigor.

**Dr Kawut:** I agree with Ray. I came back from the conference with a sense of the incredible hope that patients feel in the current day. The pace of approved therapies seems to increase every year. So while a mere 10, 15 years ago, maybe there were 1 or 2 therapies, now there's, what, 12 or 13? I lose count. That sense of hope from the patients invigorates me when I go back to my own practice.

**Dr Sager:** I echo many of the sentiments that Steve and Ray expressed. In addition, some of the most fascinating developments that I have noticed over the past several years attending the PHA conference are the increased knowledge base that the patients have developed. This is clearly evident by the breadth and depth of the questions posed to the expert panels, often stumping us. This motivates me upon my return from the conference to improve my understanding and knowledge of the details of new clinical trials and research in the field with the ultimate hope of finding a cure for this devastating disease.

**Ms Traiger:** To tag onto what Dr Sager just said, I was really impressed with the patient-led sessions that were offered. The patients are really stepping up and taking an active role in the conference now. And I think they're really doing a great job in educating their peers on pulmonary hypertension.

**Dr Benza:** There certainly is a level of sophistication that our patients have that I think is fairly unique to this group of people. For example, during the conference I passed out some surveys to get patient opinions about some risk stratification algorithms I've been working on. Not only did I get 100% of the surveys returned, unusual in itself, but in addition to having my questions answered, I received fantastic suggestions that I didn't even ask for. And so that really is a fairly good testament to the quality, enthusiasm and sophistication of the patients that we take care of.

**Dr Hemnes:** Thank you. Those are all really great points and I couldn't agree with you all more. I was also really impressed with the presentations that happened during the scientific sessions at the future of pulmonary hypertension and how fast science is moving forward in our understanding of this disease and how that is going to translate in the next decades to improved patient care. Not only just in pulmonary arterial hypertension but also in pediatric pulmonary hypertension and non-Group 1 pulmonary hypertension, which I thought was very exciting. One of the things that I thought was interesting that we were unable to put in the scientific sessions, that I think some of the people on this call might be able to help us think about, was the topic of new treatments and targets not in the pulmonary vasculature in pulmonary hypertension. And essentially, all of the presenters were talking about pulmonary vascular targets in pulmonary hypertension, because that's really where our science is right now, and especially in terms of therapeutics. But I was thinking that maybe 5 or 10 years from now a future scientific

session might be devoted to the right ventricle and treatment aimed at it in pulmonary hypertension. And I wonder if Steve or Ray, might you have any thoughts about what that conference would look like in the future?

**Dr Kawut:** Anna, that's a timely point. Corey Ventetuelo is the first author of a paper from our group, just published in *Circulation*, which showed that changes in hemodynamics, which we all consider to be the cornerstone of the understanding of this disease, actually explain very little of the impact of our effective treatments on outcomes, at least in the short term. So while we think our current treatments improve outcome because they decrease pulmonary vascular resistance or improve cardiac output (both measured at rest), that doesn't seem to be the case. This really shows how little we know about how these treatments actually work. There may be other parameters and physiologic pathways, such as the ability of the RV to mount a response to exercise, the ergoreflex, and peripheral vascular and muscular responses. There is a well-known study of a long-term PAH survivor on IV epoprostenol, which showed dramatic pulmonary vascular disease, but good right ventricular adaptation. So I think while we think we know how these drugs work (mainly by acting on the pulmonary vasculature), this may not be the case. And so 10 years down the line, we may be targeting other parameters and other systems which we're currently not, just as you say.

**Dr Benza:** Similar to what Steve was mentioning, I think the most informative conference is going to be one that doesn't isolate the pulmonary vasculature and/or the right ventricle contextually, but rather reviews this as one unit. I truly believe that the knowledge gained in the next 5 years will be driving us in a direction where tailored therapy will conjointly treat the pulmonary vasculature and the right heart. So drugs and/or drug regimens that not only reduce resistance, but also improve intrinsic right ventricular activity, and RV PA coupling is where the money is going to be. A conference designed to look at all 3 of these parameters together would be ideal as this is going to be the way we treat this disease in the not-so-distant future. As Steve mentioned, it's just not what's in the pulmonary vessels. It's the connection between the pulmonary vessels and the right heart and even the systemic skeletal musculature that's important.

**Dr Hemnes:** Thanks. I think those are important comments. And I do think, too, that there's a wealth of literature looking at mechanistically how the right heart fails that will translate into new therapeutics for the right heart in the future, and even some of that's borne fruit in clinical trials already, with trials of beta-blockers that are now we're beginning to see data from, which are exciting and interesting and may show us a way forward in how to study that better. And I agree with you, Ray, that I think linking the two—pulmonary vascular and right heart together—will be the future. And clearly, the other metrics, as well. Was there any science that was presented at the meeting that you all felt was particularly promising or exciting to you?

**Dr Sager:** I was particularly intrigued with the work that Dr Edda Spiekerkoetter is doing on the immunosuppressant drug FK-506 (Tacrolimus) as it related to BMPR2 receptor signaling. This is a commonly used drug in the transplant world and now may have an application in the field of pulmonary arterial hypertension. Edda found in her experimental lab that low-dose FK-506 reverses established pulmonary hypertension in rats and mice. Improved understanding of the BMP signaling pathway may lead to future drug development. It allows me to think differently about this condition in terms of not just simply finding a vasodilator, but something that may be an immune-modulated condition. Thinking outside the box of the conventional 3 known targeted pathways is essential for us to move forward in the field.

**Dr Benza:** As a transplant physician, knowing that these pathways intersect with others, particularly with regard to pulmonary artery remodeling, is really quite fascinating. This type of treatment paradigm could extend to other immunosuppressant regimens, including drugs like sirolimus, which also has remodeling effects on smooth muscle cells in vitro. So this "non-3 pathway thinking,"—akin to the TKI inhibitor story—is really innovative and out of the box thinking.

**Dr Hemnes:** I agree. I thought that was a really interesting new direction. And I liked the idea, too, of trying to figure out which patients that those particular agents would be useful in. And I think data like yours, Ray, from the REVEAL registry, will be helpful to figure out which are the highest risk patients that may benefit the most from a more aggressive regimen. But also on a molecular level, trying to identify patients who are likely to have, for instance, BMPR2 suppression or more profound BMPR2 suppression than your average PH patient who may benefit from FK506 or some similar agent will be useful. Have you ever thought, Ray, about applying REVEAL registry data to select patients for individual therapies?

**Dr Benza:** You know, we had thought about that many times; but we thought that those type of questions would best be answered in the form of clinical trial work because sometimes you can extrapolate too much from the databases, which might mislead you. So the answer is yes, we have thought about that and we thought it was best not to actually do that. And the interesting thing about that, Anna, is that when you look at the medications in the context of how prognosis is altered by their use, it's really in the movement of the risk factors that we monitor, not the actual drug type that's the most important thing. So, how a drug drives the change in a predictive factor, like a 6-minute walk distance, WHO functional class, or a BNP level is what changes risk, not actually the drug itself, per se.

**Dr Hemnes:** Interesting, thanks. Well, one of the other topics that came up at the scientific sessions was pediatric pulmonary hypertension, which is an important feature of our conference with

the pediatric patients and families that are there. It's also an emerging area of research and controversy. And I thought Dunbar Ivy's presentation on pediatric pulmonary hypertension and clinical trial designs in that group of patients was fascinating, particularly highlighting the challenges of sildenafil research in pediatric pulmonary hypertension. Did anyone have any thoughts on this particular field or Dunbar's presentation that was enlightening?

**Dr Benza:** As someone who just treats adult pulmonary hypertension, I love listening to talks about pediatric PH because, one, it allows me to recognize how much more difficult it is to treat children with this disease than it is adults. And, secondly, how much more we need to do in that particular field and how it really lags behind the things that we do in the adult world. So I think that's what I really got an appreciation from listening to him speak.

**Dr Hemnes:** Yes, I had similar thoughts. He did such a nice job of highlighting the challenges of studying a drug and its efficacy in the pediatric population, it really made me appreciate all the wonderful tools that we have with adults. And although there are clear limitations to a 6-minute walk, at least we do have that, and that's not even really at all useable in the pediatric population. He just did such a nice job of highlighting the tremendous challenges that physicians and patients face in that population.

**Dr Kawut:** Both for children and adults, the ultimate goal is a valid surrogate endpoint, whether it's a blood test or some other biomarker or imaging parameter, which will help you predict the effect of the therapy on the ultimate outcome. The only way to do that, of course, is to include these potential surrogates in ongoing clinical trials. Every clinical trial we execute without the insertion of some investigational surrogate endpoint is really a lost opportunity that can never be regained.

**Dr Fagan:** I think one thing that he really highlighted for me was the present day limitations that they have on determining efficacy. I was really stunned by the FDA limitation on using hemodynamics in these studies, because, as he so well pointed out, there's so little else that is something that can be applied across multiple different pediatric situations from infancy, toddlerhood, childhood, into early adolescence. The one thing that I think most of us as adults would say is, well, the hemodynamics are the things that we can use, if nothing else, at least to determine an efficacy profile of something. They're limited even by that and I found that to be really, really surprising that the FDA has mandated that that not be used as an endpoint.

**Dr Hemnes:** Yeah, I couldn't agree more. He really brought out the challenges. And it made me wonder about a path forward for pediatric pulmonary hypertension and how best to do that. And obviously, as Ray mentioned, none of us is a pediatric pulmonologist—or a pediatric pulmonary hypertension specialist. But I think of all the challenges that we as adult physicians and scientists struggle with every day, their challenges are many times greater and very important that we recognize moving forward.

**Dr Kawut:** Maybe the ideal endpoint is a patient (or parental) reported outcome. I don't think we have any validated questionnaires for pediatric pulmonary hypertension, but such an instrument could be noninvasive and clinically meaningful.

**Dr Fagan:** Yes, absolutely.

**Dr Hemnes:** I agree. And maybe also a way forward for drug approval in the future, in the absence of the other surrogate markers that you mentioned. I think that's also a kind of lead-in to my next question. I personally really enjoyed the session that Steve participated in on clinical trial design and the panel discussion during the noon session. Some of the things that I thought were really interesting about that included our colleague from the NIH who came and talked about NIH funding, particularly in the PVDOMICS grant that just recently got reviewed and also in the NIH's support for translational research, through translational program project grants and other mechanisms. I thought that the discussion that Dr McLaughlin led, with Steve and Dr Roham Zamanian, was really enlightening and opened the door for participation with a lot of members in the audience. What did you all think about the clinical trial design panel discussion? And did you have any new thoughts that came out as a result of that discussion?

**Dr Benza:** You know, unfortunately that was during my flight crisis and I missed that very engaging conversation. Although interestingly—.

**Dr Kawut:** If you missed it, how do you know it was engaging?

**Dr Benza:** Well, I'm going to tell you that right now (laughter) because that's the interesting part about it. It was so engaging that members of the audience who were there sent me video clips of what I was missing as I was stranded in the airport (laughter) via their smart phones. Now, that's a waste of perfectly good battery power. So that was quite interesting, but it did sound like it was a very worthwhile event to have witnessed.

**Dr Fagan:** I also kind of popped in it, a little bit. But I think one of the things that we need to think more broadly about is the patient outcome component to the designing of clinical trials. We all talk about that in terms of the things we're going to use to determine what makes a drug effective. I think that discussions that lead to defining effectiveness in a much more creative, patient-centered way are the things that will be important in any programs, either individual clinical trials, the PVDOMICS, you know., The other translational item to look at is what was mentioned earlier—the patient-related outcomes components to that. Ultimately, those are the most important outcomes, most of us would agree. And figuring out ways to incorporate them, not just time to clinical worsening, not just these things that can be objectively measured, but also the subjective compo-

nents in terms of the outcomes for patients I think are important. I think all of us recognize that we need to be more creative and more patient-focused in measuring the outcomes.

**Dr Benza:** Yes, Karen, that is really quite perceptive. And as I mentioned earlier, I had distributed these surveys during the conference about patient preferences. It's amazing how there is a significant population of our patients who feel they're not engaged enough in the decision-making with regard to their therapeutics and how the therapies make them feel. I think that needs to be a really critical piece of how we judge what therapeutics to use, when to use them, and should be kept in the forefront of our minds when we make these decisions.

**Dr Kawut:** As I think both Ray and Karen have pointed out, this is a multidimensional disease. To say that if we improve your PVR you're going to automatically feel better is overly reductionist, right? This is a disease that incorporates dyspnea, fatigue, anxiety, depression, weakness. People have symptoms in complicated domains which we're not particularly good at measuring or potentially even asking about. I think capturing these other important patient dimensions will be critical to really get drugs that really improve how patients feel, function, and survive.

**Dr Sager:** One of the aspects I enjoyed as part of the clinical trial design section is the issue of trial recruitment. PAH clinical trials traditionally include only small numbers of participants due to the rare nature of PAH. Hopefully with the new accreditation process of the Pulmonary Hypertension Care Centers (PHCC) through the PHA, the requirement that comprehensive care centers provide access to patients to enroll in clinical trials will increase the number and breadth of clinical trials available to patients.

**Ms Traiger:** Also, these clinical trials are going to become longer in the future. So I think a lot of us worry that we're going to run out of patients for trials, because these are not going to be 12- or 16-week trials anymore, potentially. There was also a discussion about substudies or tacking smaller studies onto larger grants, so that we could study multiple questions perhaps within one study. I think that's where the quality of life measurements can come in, as well as more patient-centered outcomes.

**Dr Hemnes:** Yes, I thought those were really important points that came out of that clinical trial design discussion. One of the things that I thought about moving forward is applying all those things that we discussed there to non-Group 1 pulmonary hypertension that I think in the future will be a greater area of research in clinical trials. And I think patient-reported outcomes are probably going to be even more important in that relatively heterogeneous population within the other non-Group 1 PH groups. They also may address some of the issues with lower numbers of patients that are in Group 1 pulmonary hypertension. So I thought those were quite relevant and fertile areas for future thoughts.

**Dr Benza:** I think that's critically important because as we all recognize, WHO Group 1 is really a very, very tiny piece of the pie. WHO Group 2 and 3 far exceed the number of people that we currently treat with PAH. And so the application of what we've learned in PAH to these broader populations, I think, would be very valuable to make sure we do it right the first time and get the answers that we want up front instead of recreating the wheel when we start doing clinical trials in those areas.

**Dr Kawut:** One of the most important things about the conference and really one of the reasons I go to it is to see people living with pulmonary hypertension in a more normal setting than in the physician's office. It is too easy that my vision of a patient with pulmonary hypertension can become someone sitting on an examining table or in the chair with me in front of the computer, trying to lamely type in a note. I think the conference is a great way of driving home the point that people with pulmonary hypertension live full lives and don't let the disease define them. Seeing people from children to seniors at meals or at parties having a good time is always very helpful to me. The conference therefore plays an important role in my relationships with my patients and in what drives me to do what I do.

**Dr Fagan:** It's absolutely important. We have now for the last 2 times had some of our PhD graduate students come to the conference just to see some of the patients living with PAH who, for them, are much more abstract ideas. And then they come to conference and they have a really tangible idea of what a PH patient looks like. It gives them a great deal of enthusiasm as they go back to continue their work. It's the graduate students who went this year, much like 2 years ago, who came back and felt tremendously invigorated and refreshed to attack their projects in the lab with a lot more meaning. So one of the things that we really enjoyed is that we've been able to do that and to get these people who are not going to have a clinical experience with a professional and, to quote one of them, he came back changed, that's the only word he could use to describe it; he felt changed.

**Ms Traiger:** I was in the sports bar when the Team PHenomenal Hope crossed the finish line. And it was really a very moving experience for me, because the room was just jam packed with mostly patients and PHA staff. It was really palpable how much that event meant to those patients—that this bicycle team went across the country basically for them. I found that very moving.

**Dr Sager:** A remarkable aspect of this year's conference that struck me that I had not experienced at previous conferences was the close attention and awareness of the international PH community to our US-based PHA organization. As most of you know, my roots are from South Africa and the South African Pulmonary Hypertension Association delegation contacted me at the conference to help develop the PH programs in South Africa. Up until only a few years ago there were *no* treatments available to patients in South Africa and

with the help and connections with PHA, they have steadily built a program. They base the development of their programs off many of the protocols we have developed here in the USA. Many countries do not have access to the research and the in-depth management or access to the latest therapies that we take for granted in the USA. This is humbling and makes one pause as we are very fortunate to have access to many more sophisticated diagnostics and therapeutic options than other countries. The world is watching us at these conferences and it was quite an eye-opener for me.

**Dr Fagan:** Along those lines, I actually attended some parts of the International Leaders Summit, which was held the day before conference. I had a chance to speak with the leaders of PHA organizations across the world. And one of the things that I really found quite interesting to our international colleagues is that this close-knit relationship that we as physicians and researchers have with our patient community is actually not the norm. In many of these countries, they have no or very, very limited engagement with their professional communities. So hopefully, that's one of the things that the rest of the world is watching for us and that we hopefully are modeling the powerful impact that having physicians, researchers, and the patient and caregiver communities interact, how we're much greater than just the sum of our parts when we do that.

**Dr Hemnes:** I think that's a wonderful comment and a really great place to stop, because I think we all are greater than the sum of our parts, and that's what this whole conference was about.